concurrent divisional applications. New claims 61 - 63 have been added by amendment. Claims 19 - 55 and 61 - 63 are thus pending.

Pursuant to a requirement for species election, claims 34 - 38, 41, 42, 44, 45, and 48 have been withdrawn pending allowance of a generic claim, 37 C.F.R. § 1.146. Claims 19 - 33, 39, 40, 43, 46, 47, 49 - 55 and 61 - 63 are thus presented for examination.

Claim amendments

Applicants amend the preamble to claim 19 in order more particularly to point out and distinctly claim the invention as a method of identifying antigen-specific T lymphocytes. New claims 61 - 63 have been added for reasons discussed later in this paper. No new matter has been added.

Invitation to provide a reference date

The Examiner has invited applicants to provide the date for Maino *et al.*, "FastImmune™ Assay System", published by Becton Dickinson Immunocytometry Systems. Applicants believe that the publication was first made available to the public in May or June of 1995.

Drawings

Applicants acknowledge the Official Draftsperson's comments on form PTO-948 attached to paper no. 17, and respectfully submit that the drawings as filed were informal and are suitable for purpose of examination. Applicants will file formal drawings upon indication of allowable subject matter.

Objection under 35 U.S.C. § 132

The Examiner has objected to applicants' amendment filed March 12, 1999 (paper no. 10) on grounds that amendment of the specification at page 5 to recite "CD40L" instead of "CD40" introduces new matter. Citing Lipsky *et al.*, *NY Acad. Sci.* 815:372-383 (1997) for the proposition that CD40 can be found on the surface of activated T cells, the Examiner argues that applicants' specification reference to CD40 as a T cell surface costimulatory molecule would not, therefore, immediately and unambiguously be recognized as intending CD40L.

Applicants acknowledge the findings cited by the Examiner, but nonetheless respectfully submit that the skilled artisan would read applicants' specification consonant with the general and accepted understanding, set forth in the opening sentences of Lipsky *et al.*, that

> [d]uring T cell-dependent B cell activation, interactions between a variety of cell surface molecules expressed by B cells and their ligands expressed by activated T cells play a role in facilitating B cell activation, proliferation, and differentiation. Prominent among these is an interaction between CD40 expressed by B cells and CD40 ligand expressed by activated T cells.

However, solely to expedite prosecution, applicants herein amend the specification at page 5 to return the original language, "CD40",[2] reserving the right

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[2] Applicants assume, for purpose of compliance with 37 C.F.R. § 1.121 (as effective November 7, 2000), that the prior amendment was entered. The replacement paragraph provided herewith is thus identical to the paragraph as originally filed, and the marked up version filed concurrently herewith demonstrates the amendment as "CD40[L]".

to address this issue in divisional or continuation applications.

Rejections Under 35 U.S.C. § 112, ¶ 1 for Inadequate Scope of Enablement are in Error and Should be Withdrawn

Acknowledging that applicants' specification has enabled the claimed methods with respect to (1) measuring intracellular expression of one or more of intracellular cytokines γ-IFN, IL-2, IL-4, IL-5, IL-10 and TNF-α;[3] (2) measuring the early activation antigen CD69; and (3) providing costimulus via CD28, CD40, CD86 or CD118,[4] the Examiner nonetheless rejects all examined claims on grounds that the specification "does not reasonably provide enablement for any intracellular cytokine, early activation or costimulus." Applicants respectfully disagree.

Although the Examiner paraphrases language that speaks to the requirements for conception[5] (and arguably

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[3] Although applicants would be delighted to accept at face value the Examiner's comment that detection of IL-5 and IL-10 are also fully enabled, applicants believe that the Examiner intended only to include as fully enabled the detection of those cytokines specifically described in applicants' specification — IL-2, IL-4, IL-13, IFN-γ, and TNF-α — and have addressed the rejection on that basis.

[4] In light of such acknowledgment, and without thereby acquiescing in the rejection, applicants add new claims 61 - 63, which are entirely free of the stated rejection.

[5] "Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g., encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that

to the requirements for written description)[6] and also uses language more appropriate to the second, rather than first, paragraph of § 112,[7]

> it appears that these comments indicate nothing more than a concern over the breadth of the disputed term. . . . Accepting, therefore, that the term is a generic one, its recitation must be taken as an assertion by appellants that all of the 'considerable number of compounds' which are included within the generic term would, as a class, be operative [in the claimed invention]. . . . The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion.

In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971).

Cytokines

With that understanding, applicants turn to the Examiner's contention that applicants' description – and indeed exemplification – of the detection of a variety of different cytokines is insufficient to enable detection of other than the specifically-exemplified species. Applicants respectfully submit that the Examiner's conclusory comment that "it is not clear how the specification as filed provides direction and guidance to

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biological property." Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016, 1021 (Fed. Cir. 1991); *quoted with approval in* Fiers v. Revel, 25 USPQ2d 1601 (Fed. Cir. 1993).

[6] University of California v. Eli Lilly and Co., 43 USPQ2d 1398 (Fed. Cir. 1997). The written description requirement of § 112, first paragraph, is separate and distinct from the enablement requirement. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991).

[7] Commenting particularly on the "metes and bounds" of the claim, M.P.E.P. §§ 706.03(d), 821, 2171, 2173.05(a), 2173.05(c), and 2173.05(d) (7th ed., rev. 1).

detecting cytokines in the instant methods other than that indicated in the specification" is insufficient "reason to doubt the objective truth of the statements contained therein" as to rise to a *prima facie* case of inadequate scope of enablement.[8] Absent an adequate *prima facie* case of nonenablement, the burden does not shift to applicants to adduce rebuttal evidence, and applicants are entitled, without more, to issuance of their claims.

Solely to expedite prosecution, however, and without admitting to the adequacy of the Examiner's *prima facie* case, applicants respectfully commend to the Examiner's attention the accompanying Declaration of Dr. Calman P. Prussin, filed concurrently herewith under 37 C.F.R. § 1.132. Dr. Prussin, an expert on the intracellular detection of cytokines, explains in the declaration why, given the skill and knowledge in the art, it would not have required undue experimentation at the time the application was filed to adapt the claimed method to detection of other cytokines. Applicants respectfully submit that the declaratory evidence is sufficient to rebut any *prima facie* case deemed established, and respectfully submit that the rejection is in error and should be withdrawn.

Early Activation Antigen

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[8] "As a matter of Patent Office practice . . . a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi, supra.*

The Examiner argues that "it is not clear how the specification as filed provides direction and guidance to detecting early activation antigens other than CD69. . . . " Applicants respectfully submit that this conclusory statement is not sufficient "reason to doubt the objective truth of the statements contained therein" as to rise to a *prima facie* case of inadequate scope of enablement and the rejection is, on that basis alone, infirm and should be withdrawn.

It is perhaps additionally appropriate here to remind the Examiner that Section 112

> [p]aragraph 1 permits resort to material outside of the specification in order to satisfy the enablement portion of the statute because it makes no sense to encumber the specification of a patent with all the knowledge of the past concerning how to make and use the claimed invention. One skilled in the art knows how to make and use a bolt, a wheel, a gear, a transistor, or a known chemical starting material. The specification would be of enormous and unnecessary length if one had to literally reinvent and describe the wheel.

Atmel Corp. v. Information Storage Devices Inc., 53 USPQ2d 1225,1230 (Fed. Cir. 1999).

> The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, hence the specification need not disclose what is well known in the art.

Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co., 221 USPQ 481, 489 (Fed. Cir. 1984). "[A] patent need not teach, and preferably omits, what is well known in the art." Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed. Cir. 1986).

The term "activation antigen", and the identity and means of detecting such activation antigens, were well known in the cellular immunology art at the time the

instant and priority applications were filed. Applicants attach hereto for the Examiner's review a copy of Cotner *et al.*, "Simultaneous flow cytometric analysis of human T cell activation antigen expression and DNA content," *J. Exp. Med.* 157:461 - 72 (1983), a reference that well antedates applicants' filing and describes the detection of a variety of activation antigens on the surface of T cells. The Examiner has proffered no reason why such other activation antigens cannot be detected, without undue experimentation, in the methods claimed by applicants; accordingly, the Examiner has failed to offer evidence counter to the objective statements of applicants' specification. Applicants respectfully submit that the rejection is in error and should be withdrawn.

Costimuli

Acknowledging applicants' earlier-filed evidence "that costimulatory activation [can be accomplished] via VLA-4 and CD5", the Examiner nonetheless argues that "it is not clear how the specification as filed provides direction and guidance to providing costimulatory activation other than targeting CD28, CD40, CD86 or CD118."

With respect, applicants submit that the Examiner has proffered no evidence contrary to the objective statements in applicants' specification or contrary to applicants' later-adduced evidence, which the Examiner has acknowledged; accordingly, applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of nonenablement, that the rejection is thus in error, and should be withdrawn.

Rejections Under 35 U.S.C. § 102 Have Been Withdrawn

Applicants thank the Examiner for his acknowledgment that the cited reference, Picker *et al.*,[9] does not disclose use of nominal antigen as a T cell stimulus in the flow cytometric detection of intracellular cytokine production, and his concomitant acknowledgment that all of applicants' examined claims are thus novel over the cited reference.

Rejections Under 35 U.S.C. § 103 are in Error and Should be Withdrawn

The Examiner rejects claims 19 - 33, 39, 40, 43, 46, 47 and 49 - 55 over Picker *et al.* in view of Seon *et al.*, Schwartz, Lolli *et al.* and/or Lolli *et al.*

In response, applicants respectfully commend the Examiner's attention to the declarations under 37 C.F.R. § 1.132 of Dr. John Altman and Dr. Calman Prussin, that speak to the nonobviousness of applicants' claimed invention. In light of such evidence, applicants respectfully submit that the rejection is in error and should be withdrawn.

CONCLUSION

Applicants respectfully submit that the examined claims are in good and proper form for allowance. Applicants thus respectfully request that those species claims withdrawn pursuant to election of species be rejoined, examined, and also held allowable. Applicants invite the Examiner to call the undersigned attorney of record if any outstanding matter might be

[9] Picker *et al.*, *Blood* 86:1408-1419 (1995).

resolved most expeditiously by way of telephonic conference.

DEC 2000

Respectfully Submitted,

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Enclosures:

- the Declaration of John D. Altman, Ph.D., under 37 C.F.R. § 1.132;
- the Declaration of Calman P. Prussin, M.D., under 37 C.F.R. § 1.132;
- Supplemental information disclosure statement, PTO-1449, and identified references

Attachments:

- Appendix A, containing a marked up copy of the amended claims pursuant to 37 C.F.R. § 1.121(c)(1)(ii) (as amended) and a marked up copy of the specification replacement paragraph pursuant to 37 C.F.R. § 1.121(b)(iii); and

- Appendix B, containing a copy of Cotner *et al.*, "Simultaneous flow cytometric analysis of human T cell activation antigen expression and DNA content," *J. Exp. Med.* 157:461 - 72 (1983)

P-3639P1/BDIS-3CIP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Maino *et al.*
Serial No.	:	08/803,702
Filed	:	February 21, 1997
For	:	METHOD FOR DETECTING T CELL RESPONSE TO SPECIFIC ANTIGENS IN WHOLE BLOOD
Art Unit	:	1644
Examiner	:	Phillip Gambel, Ph.D.

Palo Alto, CA
December 1, 2000

Hon. Assistant Commissioner
for Patents
Washington, D.C. 20231

Appendix A
Filed Pursuant to 37 C.F.R. § 1.121

IN THE SPECIFICATION:

In the concurrently filed Preliminary Amendment, applicants have instructed that the paragraph beginning on page 4, line 24 and ending on page 5, line 13, of applicants' specification be deleted and replaced. Amendments within the replacement paragraph are as follows:

More specifically, this invention provides an assay protocol using whole blood for the rapid (generally less than 24 hours, preferably less than 6 hours), highly efficient, Ag-specific activation of secretion-inhibited CD4+

(memory/effector) T cells, followed by the quantization and characterization of these Ag-specific T cells using multiparameter flow cytometric, immunofluorescent detection of one or more intracellular cytokines (including IL-2, IL-4, γ-IFN and TNF-α) and an early activation antigen (such as CD69), in combination with one or more T cell subset-defining phenotypic markers (such as CD3 or CD4). It is further disclosed that the antigen specific response can be more easily detected when the antigen stimulation is provided in conjunction with costimulation of surface antigens involved with accessory cell surface molecules, such as CD28, CD40**[L]**, VLA-4, and other such specificities known in the art. Costimuli can be either antibodies or ligand binding to these antigens. A preferred costimulus is CD28. It is also determined that T cell responses measured using the protocol defined in this disclosure can be shown to be sensitive to drugs which have been demonstrated to augment or suppress cellular responses (e.g., exogenous cytokines, cyclosporin-A, herbimycin-A).--

IN THE CLAIMS:

In the concurrently filed preliminary amendment, applicants have instructed that claim 19 be amended by rewriting. Amendments within claim 19 are as follows:

19 (once amended). A method of detecting **[antigen-specific cytokine production by individual]** **antigen-specific** T lymphocytes, comprising**[the steps of]**:

contacting a sample containing peripheral blood mononuclear cells with an MHC-dependent nominal antigen;

adding to said sample an inhibitor of cytokine secretion;

adding to said sample at least one cytokine-specific antibody and at least one T lymphocyte subset-defining antibody; and then

flow cytometrically detecting the intracellular binding of said cytokine-specific antibody by cells in the defined T lymphocyte subset.

Respectfully Submitted,

DEC 2000

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